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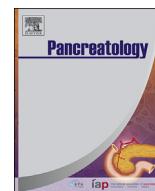
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International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club

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ABSTRACT

Background/objectives: This paper is part of the international consensus guidelines on chronic pancreatitis, presenting for interventional endoscopy.

Methods: An international working group with experts on interventional endoscopy evaluated 26 statements generated from evidence on 9 clinically relevant questions. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to evaluate the level of evidence. To determine the level of agreement, a nine-point Likert scale was used for voting on the statements.

Results: Strong consensus was obtained for 15 statements relating to nine questions including the recommendation that endoscopic intervention should be offered to patients with persistent severe pain but not to those without pain. Endoscopic decompression of the pancreatic duct could be used for immediate pain relief, and then offered surgery if this fails or needs repeated endoscopy. Endoscopic drainage is preferred for portal-splenic vein thrombosis and pancreatic fistula. A plastic stent should be placed and replaced 2–3 months later after insertion. Endoscopic extraction is indicated for stone fragments remaining after ESWL. Interventional treatment should be performed for symptomatic/complicated pancreatic pseudocysts. Endoscopic treatment is recommended for bile duct obstruction and afterwards surgery if this fails or needs repeated endoscopy. Surgery may be offered if there is significant calcification and/or mass of the pancreatic head. Percutaneous endovascular treatment is preferred for hemosuccus pancreaticus. Surgical treatment is recommended for duodenal stenosis due to chronic pancreatitis.

Conclusions: This international expert consensus guideline provides evidenced-based statements concerning indications and key aspects for interventional endoscopy in the management of patients with chronic pancreatitis.

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Introduction

Interventions for chronic pancreatitis (CP) may include endoscopy and extracorporeal shock wave lithotripsy (ESWL) as well as surgery, but with a wide variation in practice globally for these various approaches [1,2]. There are several guidelines focusing on interventional endoscopy in chronic pancreatitis [3–7]. However, these previous guidelines on CP have tended to be based on one professional group and/or a single geographical area. The purpose of these guidelines was to provide internationally applicable recommendations for practicing clinicians on the indication, selection and approaches for non-surgical interventions. Multidisciplinary experts from the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (IAP-APA-JPS-EPC) joined to minimize intrinsic biases for making The International Consensus Guidelines on Chronic Pancreatitis (ICGCP). This paper aimed to be part of the international consensus guidelines on chronic pancreatitis, presenting for interventional endoscopy.

Methods

The process for developing the ICGCP guidelines was commenced at the EPC Annual Meeting of 2016. A team of world-wide experts comprising gastroenterologists, surgeons and radiologists with expertise in endoscopy and interventional radiology as well as surgery was composed, chaired by Masayuki Kitano. International experts were selected from members of ICGCP Committee composed of four societies: EPC, APA, JPS and IAP (Supplementary table). The first step was to generate clinical questions and evaluate the evidence. A literature review of invited expert reviews, systematic reviews, and landmark papers that were published on CP was performed by 11 guideline members (MK, TMG, PKG, TI, AI, HI, AK, KT, IY, SI, TS). The 11 guideline members raised as many clinical questions as possible, and consolidated them to a smaller number. For each clinical question, several statements were made. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to

evaluate the level of evidence per statement (see <http://www.uptodate.com/home/gradingtutorial>). Quality assessment of evidence was graded as 'high' if there was (very) low probability of further research substantially changing the conclusions, 'moderate' if further research might completely change the conclusions, and 'low' if further research was likely to completely change the conclusions. Statements were revised by discussion among all guideline members for each domain requiring multiple iterations until there was complete agreement. Overlapping concepts in different statements were consolidated into a smaller number of statements. The strengths of the recommendation were graded as 'strong' if it was very certain that benefits outweigh risks and burdens, 'weak' if risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain, or 'conditional' if it was in between strong and weak recommendation.

After grading, the working group of all guideline members voted on each statement for strength of agreement, using a nine-point Likert scale. A single round of voting was completed using an anonymized web-based system, and statements were not further modified following voting. Out of the results, a Cronbach's alpha reliability coefficient was calculated per statement (<http://hdl.handle.net/1805/344>). The voting results were classified for agreement as either; 'strong' if 80% of votes were 7 or above, 'conditional' if 65%–80% of votes were 7 or above, and 'weak' less than 65% of votes were 7 or above. In addition, comments to each question and statements were compiled to explain the surrounding issues, supported by key references.

Results

Q 1: What are the indications for intervention in chronic pancreatitis.

Statement 1.1. Endoscopic or surgical treatment should be offered to patients with chronic pancreatitis with persistent severe pain. Intervention in the form of either surgery or endotherapy is not recommended in asymptomatic patients with chronic pancreatitis who do not have abdominal pain to improve pancreatic exocrine and/or endocrine function or

prevent cancer.*Quality assessment: moderate**Recommendation: strong**Agreement: strong* $\alpha = 1.00$

Statement 1.2. Endoscopic or surgical treatment should be carried out after careful patient selection for local complications of chronic pancreatitis with persistent clinical symptoms such as gastric outlet obstruction, duodenal stenosis, biliary obstruction with cholestasis and pseudocysts.

*Quality assessment: moderate**Recommendation: strong**Agreement: strong* $\alpha = 1.00$

Statement 1.3. Celiac plexus block may be undertaken in patients for significant abdominal pain who are not candidates for pancreatic surgery, or have not responded to endotherapy and extracorporeal shock wave lithotripsy (ESWL), or have a poor general condition as a temporizing measure before definitive therapy.

*Quality assessment: moderate**Recommendation: weak**Agreement: weak* $\alpha = 0.41$ **Comment**

Although pain is the reason for intervention and key to deciding timing and type of intervention there is no consensus on how to assess pain in chronic pancreatitis, but there are several recommendations by the ICGCP for the understanding and management of pain in chronic pancreatitis [1]. In the clinical situation pain will normally be rated on an eleven-point numerical scale ranging from 0 (no pain at all) to 10 (worst imaginable pain). Pain characteristics requiring intervention are that (1) there should be a plausible relationship between pain and ductal morphology as in large pancreatic duct disease, (2) the pain is persistent and continuous with or without exacerbations, (3) that medical treatment is not successful, and (4) that pain should last for more than three months. The likelihood for successful treatment depends on many factors including age, duration of disease, pain characteristics, and opioid dependency [2]. Persistent severe pain requires that it should last for >3 months (i.e. chronic pain according to the new ICD-11 guidelines), and whilst pain is a composite of sensory intensity, cognitive and affective factors that need to be taken into consideration for the individual patient, but pain intensity above 3 on the numerical scale with impact on daily life is normally considered severe [8]. Many factors can bring on pancreatic pain and shall be considered in the evaluation [9]. Long pain duration may affect the outcome in a negative way as the sensory system can undergo permanent neuroplastic changes where pain may become independent on the peripheral nociceptive drive [10]. More importantly a temporal association between the development of pancreatic morphological changes and pain may predict a favorable prognosis to invasive treatments [2].

It is the general impression that patients with central sensitization do not respond adequately to treatment [10]. However, central sensitization is difficult to measure and although quantitative sensory testing, electrophysiological and imaging methods may reveal some proxies for permanent neuroplastic changes in the central nervous system, there are no accepted criteria to evaluate these findings. Other factors such as anxiety and cognitive features goes hand in hand with central sensitization and complicates evaluation of the individual patient [1]. Narcotic dependence normally goes hand in hand with long-lasting pain and central

sensitization and opioid use is associated with a less favorable outcome [11,12]. It is also of concern that opioids can in some instances contribute to hyperalgesia [8,13]. However, in the individual patient, it is difficult to determine whether opioids worsen the response to treatment as these patients have more severe pain and lower quality of life. This predicts a bad outcome to treatment per se and complicates the evaluation [2].

Once medical measures have failed, persistent severe pain can be treated by both endoscopic and surgical procedures, although pancreatic function may not always be improved [14–21]. Early surgery in two randomized trials was associated with an increased likelihood of complete pain relief associated with a reduced risk of pancreatic insufficiency and low re-intervention rates compared to endoscopic intervention [20,21]. Symptomatic local complications of chronic pancreatitis including gastric outlet obstruction, duodenal stenosis, biliary obstruction with cholestasis and pseudocysts are also indications for interventional treatment [15,19–22].

Celiac plexus block (CPB) consists of injecting corticosteroids, local anesthetics or absolute alcohol into the celiac plexus nerve/ganglia to disrupt the signaling of painful stimuli through pancreatic nerves [23]. Meta-analyses have reported that EUS-guided CPB may relieve pain in 51%–59% of patients but this is short-lived and is inferior to surgical management [24–26]. The nerve destruction may lead to an increase in pain due to neuropathic mechanisms that develop later and there are potential severe side effects such as hypotension, hemorrhage, infections and neurological complications [2,27]. CPB lasts for <3 months and after the neurolysis any neuropathic pain will worsen and together with the potential severe side effects neurolysis is a contraindication in chronic pancreatitis [28]. Therefore, we were unable to reach a consensus about CPB for management of pain in patients with chronic pancreatitis.

Q 2: What is the best strategy for the treatment of pancreatic ductal stricture.

Statement 2.1. Non-surgical decompression of the main pancreatic duct including endoscopic therapy can be selected for immediate pain relief of chronic pancreatitis before considering surgery. Surgical intervention should be considered if endoscopic procedure fails or has temporary success needing repeated endoscopic therapy.

*Quality assessment: moderate**Recommendation: conditional**Agreement: strong* $\alpha = 0.88$

Statement 2.2. If there are contraindications for surgical therapy in patients in whom conventional endoscopic therapy has failed, endosonographic-guided drainage of the pancreatic duct is another option for pain control.

*Quality assessment: moderate**Recommendation: weak**Agreement: weak* $\alpha = 0.47$

Statement 2.3. Endoscopic drainage should be the preferred modality for treating pancreatic pain and biliary stricture in patients with chronic pancreatitis who have associated portal/splenic vein thrombosis.

*Quality assessment: moderate**Recommendation: conditional**Agreement: strong* $\alpha = 0.82$

Comment

The main purpose of main pancreatic duct (MPD) decompression is pain relief [29–38]. The immediate response rates with endoscopic stenting range from 65% to 95% [16,18,29–38]. Morbidity rates of 18%–58% and mortality rates of 0–5% are reported for both endoscopy and surgery [11,20,21,39–43]. The long-term pain relief is 54% at 2 years [5], 85% at 2–12 years [29], 64% at 2 years [18], and 58% at 12 years [36]. Failed stone extraction using endoscopic pancreatic sphincterotomy and a basket or a balloon is associated with stones >10 mm, diffuse location, stone impaction, and location upstream from a stricture [44,45]. The success rate of endoscopic therapy is much higher for strictures and stones in the head of the pancreas than either the body and/or the tail of the pancreas [4,19].

Three randomized trials demonstrated that surgery is more effective than endoscopic treatment for persistent pain relief [20,21,43,47]. In the randomized controlled study from the Czech Republic, the initial success rates were similar for both groups, but at the 5-years, absence of pain weight gain were more frequent in the surgical group although the partial relief of pain and new-onset diabetes mellitus were not significantly different [20]. In the randomized trial from the Netherlands, symptomatic patients who underwent endoscopic treatment as the initial treatment for MPD obstruction had less pain relief (32% vs 75%, at 2 years; 38% vs 80%, at 5 years respectively), with more procedures (median of 12 versus 4 at 5 years respectively), than patients who were treated surgically [21,43]. Moreover, 47% of the patients in the endoscopy group eventually underwent surgery after 5-years follow-up [44]. The ESCAPE multicenter, randomized trial comprised 88 patients with chronic pancreatitis, a dilated MPD, and who had only recently started using prescribed opioids for severe pain (strong opioids for <2 months or weak opioids for ≤6 months) [46]. In the early surgery group 44 patients underwent pancreatic drainage surgery within 6 weeks after randomization and in the endoscopy-first approach group 44 patients were randomized to medical treatment, endoscopy including lithotripsy if needed, and surgery if needed. During 18 months of follow-up, patients in the early surgery group had a lower Izbicki pain score than patients in the group randomized to receive the endoscopy-first approach group (37 versus 49). Complete or partial pain relief at end of follow-up was achieved in 23 (58%) of 40 patients with early surgery compared to 16 (39%) of 41 in the endoscopy-first group. The total number of interventions was lower in the early surgery group, although treatment complications, mortality (0%), hospital admissions, pancreatic function, and quality of life were not significantly different between early surgery and the endoscopy-first approach [46]. Hirota et al. also found that endoscopic stent placement when necessary for more than one year, was inferior to surgery [47]. These studies require cautious interpretation pending controlled sham clinical trials [2].

In complex cases when surgical and conventional endotherapy are not possible, then EUS-guided drainage of the MPD may be an option for pain control with an overall clinical success rate of 78.8%, but the adverse event rate (abdominal pain, bleeding, perforation, fever and severe pancreatitis) of 18.9% with a median (range) stent patency of 195 (10–780) days [48–54]. More recent developments include the use of a dedicated plastic stent or a fully covered self-expandable metal stent (FCSEMS) [55,56]. EUS-guided drainage of the MPD should only be performed at a center of expertise, preferably in the context of a clinical trial.

Splanchnic venous thrombosis including splenic vein, hepatic portal vein and mesenteric vein thrombosis leading to extrahepatic portal hypertension in patients with CP has prevalence of around 11.6% [57]. Endoscopic therapy may be appropriate in this situation

as venous collaterals confer a major risk of complications from surgery [58].

Q 3: How should endoscopic stent treatment be done for pancreatic ductal stricture.

Statement 3.1. A straight plastic pancreatic stent should be placed across the stricture depending on the caliber of the stricture of the pancreatic duct.

Quality assessment: low

Recommendation: conditional

Agreement: strong

$\alpha = 0.88$

Statement 3.2. An endoscopic retrograde cholangiopancreatography (ERCP) inserted endoscopic stent should be removed or exchanged at between 2 and 3 months later. At this time a new stent should be inserted if there is still a significant stricture.

Quality assessment: low

Recommendation: conditional

Agreement: strong

$\alpha = 0.88$

Statement 3.3. Multiple stents or a metal stent may be considered for persisting pancreatic strictures due to severe chronic pancreatitis.

Quality assessment: low

Recommendation: conditional

Agreement: weak

$\alpha = 0.47$

Comment

Around 36% of patients who receive pancreatic stenting develop ductal changes, which are related either to stent occlusion and direct stent trauma or side branch occlusion [59,60]. Stent replacement is commonly performed 2–6 months after the initial stent insertion and not be for >1 year [30–34,36–38,43,47,61–65].

Multiple plastic stents [35], or a removable FCSEMS have been used to try to achieve quicker stricture resolution [66–68]. Costamagna et al. found that after a median of three plastic stents (8.5-Fr to 11-Fr) placed for a mean of 7 months resulted in 84% of patients being asymptomatic without major complications during a mean follow-up of 38 months [35]. FCSEMS placement for 2–3 months produced complete pain relief in 86% at a mean follow-up of 5 months after stent removal but there was a high stent migration rate [66–68]. However, we were unable to reach a consensus about multiple stents or a metal stent for treatment of persisting pancreatic strictures due to severe chronic pancreatitis, because these previous studies were non-randomized.

Q4: What is the strategy for the treatment of pancreatic ductal stones.

Statement 4.1. ESWL should be the first-line therapy as non-surgical intervention for main pancreatic duct stones in patients with chronic pancreatitis who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain.

Quality assessment: low

Recommendation: conditional

Agreement: conditional

$\alpha = 0.71$

Statement 4.2. Endoscopic extraction is indicated for small stones or stone fragments after ESWL.

Quality assessment: moderate

Recommendation: conditional

Agreement: strong

$\alpha = 0.82$

Comment

ESWL for MPD stones >5 mm has achieved complete pain relief in 52.7% of patients who failed conservative pain management and mild to moderate pain relief in 33.4% at a median (range) of 24 (2–60) months follow-up [69]. Quality of life improved in 88.2% and complete ductal clearance was achieved in 70.7% patients [69]. Adverse events from ESWL can be achieved in <6.0% of patients treated [14,70,71].

A randomized controlled study that compared ESWL alone with ESWL plus endoscopic stent placement revealed no difference between the groups neither in terms of MPD diameter decrease, nor in the number of pain episodes/year [70]. Endoscopic intervention alone for pancreatic duct stones has a low success rate and a high complication rate [72]. There are however some studies that showed that combined ESWL and endoscopic therapy might provide favorable long-term results [73], even with coexisting pancreatic pseudocysts [74]. Intraductal laser or electrohydraulic lithotripsy is another option, but success rates vary from 47% to 89% [75,76]. Although there was no study comparing ESWL and intraductal therapies for treatment of pancreatic stones, intraductal therapies require insertion of a pancreatoscope into the pancreatic duct [77–81]. Further study is needed to decide whether these intraductal therapies can replace ESWL as first-line treatment.

Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.

Statement 5.1. For pancreatic pseudocysts that cause symptoms and/or complications, interventional or surgical treatment should be performed.

Quality assessment: moderate

Recommendation: strong

Agreement: strong

$\alpha = 0.94$

Statement 5.2. Underlying stricture or disruption of the main pancreatic duct with symptoms and/or complications should be treated with endoscopic transpapillary placement of a pancreatic stent for pseudocysts <5 cm and with communication with the main pancreatic duct.

Quality assessment: moderate

Recommendation: conditional

Agreement: conditional

$\alpha = 0.71$

Statement 5.3. Asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter that do not resolve within six weeks may be treated with transmural drainage.

Quality assessment: low

Recommendation: weak

Agreement: weak

$\alpha = 0.53$

Statement 5.4. In case of a suspected neoplastic cystic lesion diagnostic needle aspiration of the cyst may be done.

Quality assessment: low

Recommendation: weak

Agreement: weak

$\alpha = 0.53$

Statement 5.5. Surgical intervention should be considered if endoscopic drainage of pseudocysts fails or has temporary success needing repeated endoscopic therapy, especially when there is disconnected duct syndrome, inflammatory mass, and intraductal calculi with duct strictures.

Quality assessment: low

Recommendation: conditional

Agreement: strong

$\alpha = 0.82$

Comment

Pancreatic pseudocysts occur in 20% and 40% of patients with CP [82]. Potential complications of the pseudocysts include infection of the pseudocyst, bile duct or gastric outflow obstruction or duodenal stenosis, rupture into the peritoneal cavity, pancreato-pleural fistula, portal or splenic vein thrombosis leading to sinistral (left-sided) portal hypertension, pseudocyst erosion into adjacent vessels resulting in pseudoaneurysm formation, and bleeding into the gastrointestinal tract or peritoneal cavity [82,83]. MPD disruption and stricture may lead to delayed resolution or recurrence of pancreatic pseudocyst in patients with CP.

Pancreatic duct stenting may improve clinical outcomes in patients with pancreatic duct stricture or leakage [84]. When the pseudocyst communicates with the MPD, transpapillary approach is initially recommended. This approach is useful for drainage of pseudocysts measuring <5 cm that are not suitable for transmural drainage [85]. Therefore, if pancreatic duct stricture or disruption is suspected on imaging tests such as CT and MRI, then endoscopic retrograde pancreatography (ERP) is recommended with pancreatic duct stenting across the stricture or disruption prior to pseudocyst drainage. In cases with large pseudocysts however, ERP may be difficult owing to the severe luminal compression of the stomach or duodenum, so transmural drainage should be performed first. For larger pseudocysts, endoscopic transmural drainage has a technical success rate of more than 90% and a treatment success rate of 75–90% [86]. For transmural drainage, EUS-guided drainage has mostly replaced conventional endoscopy-guided drainage, as needle puncture can be made more accurately and more safely by avoiding any interposed vessel under real-time color Doppler guidance [87,88].

Spontaneous resolution of pseudocysts in patients with CP may occur in around 20% of cases whilst independent predictive factors of persisting symptoms are intrapancreatic pseudocysts greater than 4 cm or if they are extra-pancreatic [89]. Indications for prophylactic pseudocyst drainage in the absence of symptoms include compression of major vessels, pancreato-pleural fistula, pseudocyst size >5 cm without any regression after >6 weeks, pseudocyst wall >5 mm, and pseudocysts associated with advanced MPD changes or pancreatolithiasis [3,4]. However, we were unable to reach a consensus about transmural drainage for asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter because of low level of evidence.

Differentiation between a pseudocyst and a cystic pancreatic neoplasm is essential [90–92]. The pooled sensitivity (54%) for diagnostic needle aspiration of the cyst is low, with a 2.7% morbidity rate [93,94]. Therefore, we were unable to reach a consensus about diagnostic needle aspiration of the cyst for a suspected neoplastic cystic lesion.

There are four randomized trials comparing endoscopic with surgical intervention that showed that both approaches provided similarly effective treatment for the pancreatic pseudocysts with no significant differences in mortality [87,88,95,96]. Endoscopic drainage was superior in terms of short-term quality of life, duration of hospital stay, the frequency of adverse events, and hospital costs, although there was a greater need for additional invasive procedures with endoscopy-based compared to open surgical drainage. Endoscopic drainage may be preferred to surgical treatment in symptomatic or complicated non-hemorrhagic pancreatic pseudocysts [5,82,84,97,98]. Endoscopic drainage of hemorrhagic pseudocysts is contraindicated requiring a combined endovascular and surgical approach [3,5,82]. Surgery should be undertaken if

endoscopic drainage is not successful [3,5,82].

Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.

Statement 6.1. Endoscopic treatment is recommended when the patients show symptoms related to the distal bile duct obstruction (obstructive jaundice and/or acute cholangitis), and in persistent cholestasis with alkaline phosphatase elevation (>2–3 times) for at least month even in asymptomatic patients.

Quality assessment: low

Recommendation: conditional

Agreement: strong

$\alpha = 0.88$

Statement 6.2. Endoscopic treatment with multiple plastic or covered metal stents may be effective for relieving of the symptoms related to the distal bile duct obstruction due to chronic pancreatitis.

Quality assessment: low

Recommendation: weak

Agreement: conditional

$\alpha = 0.71$

Statement 6.3. In main biliary duct strictures caused by chronic pancreatitis, biliary stent placement is recommended for a period of 6 months to 1 year.

Quality assessment: low

Recommendation: weak

Agreement: Weak

$\alpha = 0.65$

Statement 6.4. Plastic stent replacement for main biliary duct stricture is recommended every 3 months. The optimal period for replacement of covered metal stent is currently unknown.

Quality assessment: low

Recommendation: weak

Agreement: Conditional

$\alpha = 0.71$

Statement 6.5. Endoscopic placement of multiple plastic or covered metal stent and/or surgery are appropriate to manage refractory bile duct obstruction.

Quality assessment: low

Recommendation: conditional

Agreement: conditional

$\alpha = 0.76$

Statement 6.6. Surgical treatment should be planned if bile duct obstruction reoccurs after one year of endoscopic stent treatment. For the patients who have significant calcifications and/or mass of the pancreatic head, surgical treatment may be preferred as an initial treatment.

Quality assessment: low

Recommendation: strong

Agreement: strong

$\alpha = 0.94$

Comment

Asymptomatic cholestasis due to intra-pancreatic bile duct stricture may improve spontaneously during observation, but secondary biliary cirrhosis may develop due to continuous cholestasis [15]. Endoscopic stenting for biliary decompression is required in patients with CP presenting with a ≥ 4 -week history of biliary obstruction with jaundice, and/or asymptomatic elevation of serum alkaline phosphatase >2 times the upper limit of normal [4]. Smits et al. reported good short-term results, but only 27.6% long-term success [33]. Calcific pancreatitis is a predictive factor for failure of initial treatment with single plastic stent, and in these cases, surgical treatment is preferred as an initial treatment [99,100].

Multiple plastic stents [101,102], or a covered SEMS may be used to manage the refractory cases [66,103,104]. Endoscopic biliary stenting has no additional effect beyond one year [3,4,33,104–106]. Surgical treatment should therefore be planned if bile duct obstruction recurs after one year of stent therapy [105,106]. Early surgical intervention benefits patients in terms of better pain control and preservation of pancreatic function [40,46,107]. A resection must be undertaken if malignancy cannot be excluded.

Biliary stricture in calcified CP is difficult to resolve [99,100]. Randomized studies have shown better efficacy of SEMS compared to multiple plastic stents in treating benign biliary strictures and need be exchanged every 3–12 months [108,109]. However, there were low level of evidence about how we should perform endoscopic treatment for main biliary duct obstruction in chronic pancreatitis. In particular, we were unable to reach a consensus about the duration of stent placement.

Q7: What is the strategy for the treatment of internal pancreatic fistula and pancreatic pleural effusion and ascites in chronic pancreatitis.

Statement 7.1. Endoscopic interventional therapy should be undertaken for the management of internal pancreatic fistula in patients presenting with main pancreatic duct disruption or obstruction.

Quality assessment: low

Recommendation: conditional

Agreement: Strong

$\alpha = 0.88$

Comment

Endoscopic interventional therapy for internal pancreatic fistulas such as pancreato-peritoneal and pancreato-pleural fistulas in CP, includes trans-papillary pancreatic stenting, and endoscopic sealing of pancreac fistula using glue [110–113]. Early bridging of the MPD by pancreatic stent can lead to satisfactory outcome provided this is done before the internal fistula develops are permanent fistula tract by granulation tissue and fibrosis [113]. Surgical therapy will be required in patients with complete MPD obstruction or disruption, or when there is an established internal fistula [110].

Q8: What is the strategy for the treatment of hemosuccus pancreaticus in chronic pancreatitis.

Statement 8.1 Percutaneous endovascular treatment should be the first choice of treatment for hemosuccus pancreaticus in hemodynamically stable patients. However, patients with hemodynamic instability and unsuccessful embolization should undergo surgery.

Quality assessment: low

Recommendation: conditional

Agreement: strong

$\alpha = 0.94$

Comment

Hemosuccus pancreaticus is a rare form of intermittent gastrointestinal blood loss, defined as bleeding into the duodenum from an internal vascular fistula between a vein or an artery with the MPD, most commonly due to a pseudoaneurysm [114,115]. Endovascular therapy is preferred ahead of surgery although placing a stent in the MPD may also work in blocking the fistula. The success rate of angiographic embolization as the initial therapy is over 70% whilst surgery tends to be nearly always successful there is a small risk of post-operative death [115,116].

Q9: What is the strategy for the treatment of duodenal obstruction in chronic pancreatitis.

Statement 9.1. Surgical treatment is recommended for duodenal stenosis associated with chronic pancreatitis, as endoscopic treatment is difficult in such cases.

Quality assessment: moderate

Recommendation: conditional

Agreement: strong

$\alpha = 0.88$

Statement 9.2. Duodenal stenosis due to chronic pancreatitis should be carefully differentiated from pancreatic cancer.

Quality assessment: moderate

Recommendation: strong

Agreement: strong

$\alpha = 1.00$

Comment

Around 5% of patients with CP have duodenal stenosis due to inflammation of the pancreatic head or groove pancreatitis, which occurs locally in the groove formed by the duodenum, pancreatic head, and common bile duct [15,117]. Groove pancreatitis accounts for around 6% of CP cases and up to 20% of patients with CP who are treated by partial pancreaticoduodenectomy [117]. ERCP is technically challenging in bile or pancreatic duct stenosis with concurrent duodenum stenosis [44], and EUS-guided drainage of the MPD or the main biliary duct may be an alternative approach [118]. Surgical intervention is preferred in patients with biliary and pancreatic duct strictures due to CP accompanied by duodenal stenosis but cancer must be excluded [15,119].

Discussion

The aim of the ICGCP (EPC-APA-JPS-IAP) is not only to assist a more pragmatic basis for patient diagnosis and management but also to help accelerate the assessment and hence the development of newer pharmacological and other therapies. The advantage of ICGCP over the other guidelines is to provide internationally applicable recommendations. Regarding interventional endoscopy, previous guidelines on CP have tended to be based on one professional group and/or a single geographical area [17–20]. By tackling evidence based multi-disciplinary approach across different professional organizations and different continents intrinsic biases can be minimized. In addition, most previous guidelines included interventional endoscopy as a part of therapy. Therefore, detailed statements for interventional endoscopy were not described in these guidelines. The European Society of Gastrointestinal Endoscopy (ESGE) reported guidelines specific to interventional endoscopy on CP, in which statements for indications, strategy and methods were created only by endoscopists. The current guidelines of ICGCP are different from ESGE guidelines in that surgeons and endoscopists from all major continents contributed to creating detailed statements.

Nine key clinically relevant questions with 26 statements were eventually chosen to be evaluated. Of these a strong consensus was obtained for 15 statements relating to nine questions (Table 1). A key recommendation was that intervention either non-surgical or surgical should be offered to all patients with persistent severe pain and large duct disease refractory to medical management. This is in line with the ICGCP guidelines for surgery and the timing of intervention in CP [120]. Even so at present there is no consensus on how to assess pain in CP [1,2,8,9]. Whilst many factors can bring on pancreatic pain [9], previous ICGCP guidelines have made a number several recommendations for the understanding and management of pain in CP [1]. It is important to recognize that long term opioid use is associated with pain of long duration and is associated with a less favorable

outcome in part due to central sensitization [11,12,107]. Intervention whether by endoscopic therapy or surgery is better undertaken sooner rather than later. Early surgery for pain is especially effective [11,40,46]. Surgery is also an effective treatment for pancreatic ductal stones compared to endoscopy therapy [20,21]. Non-surgical decompression of the MPD however could be used for immediate pain relief, and then the patient offered surgery if this failed. Endoscopic drainage is preferred for biliary stricture if there is associated hepatic portal-splenic vein thrombosis. In terms of endoscopic techniques, a straight plastic stent should be placed across a pancreatic stricture and stricture dilatation could then be undertaken depending on the degree of narrowing; an endoscopic stent should be removed or replaced 2–3 months later after insertion; and endoscopic extraction is indicated for stone fragments following ESWL. Patients with a symptomatic pancreatic pseudocyst and/or associated with complications should be offered surgical or non-surgical intervention. Endoscopic treatment is recommended for obstructive jaundice and/or acute cholangitis due to distal bile duct obstruction and then surgery if this fails. Surgery may be offered if there is significant calcification and/or mass of the pancreatic head. Endoscopic intervention is preferred for an internal pancreatic fistula. Percutaneous endovascular treatment is preferred for hemosuccus pancreaticus. A duodenum preserving head resection is recommended for duodenal stenosis due to a CP in the head of the pancreas.

Although there was a strong recommendation for the use of endoscopic treatment for obstructive jaundice and/or acute cholangitis due to distal bile duct obstruction, there was only conditional agreement for the use of biliary stents to manage uncomplicated or even refractory bile duct obstruction. There was also conditional agreement on all three statements relating to how endoscopic biliary drainage could technically be best achieved. There was conditional support for the use of ESWL with MPD stones in patients to relieve pain who do not obtain adequate pain relief with pancreatic duct stent placement. Conditional support highlights the need for more focused research on these questions.

There was strong support that symptomatic pancreatic pseudocyst should be offered surgical and/or non-surgical intervention. There was however, only conditional support using endoscopic pancreatic stents for pseudocysts <5 cm, irrespective of associated strictures and other features. Also there was only weak support for transmural drainage of asymptomatic and uncomplicated pancreatic pseudocysts >5 cm in diameter that do not resolve within six weeks, or diagnostic needle aspiration of suspected neoplastic cystic lesion in the presence of CP.

There was only weak agreement on the use of celiac plexus block to be undertaken in patients with significant abdominal pain who are not candidates for pancreatic surgery, or in those who have not responded to endotherapy and ESWL, or in those who have a poor general condition as a temporizing measure before definitive therapy. Pain relief only lasts for short term with a risk for side effects such as postural hypotension and diarrhea [28]. Another major concern is that the use of celiac plexus block can cause severe inflammation and fibrosis making subsequent surgery quite difficult and so celiac plexus block should be abandoned, in line with the ICGCP consensus guidelines for the understanding and management of pain in CP [1]. There was weak agreement endosonographic-guided drainage of the pancreatic duct is an option for pain control even if there are contraindications for surgical therapy in patients in whom conventional endoscopic therapy has failed. This was based on the fact that evidence to support this approach is weak, whilst there are potential serious complications. There was also lack of support for the use of multiple stents or a metal stent for persisting pancreatic strictures, due to lack of good evidence. The current evidence base does not support strong recommendations related to the application of endoscopy or surgery

Table 1
Recommendations stratified according to the α score.

Domain	Statement	α score	Quality assessment	Recommendation	Agreement
Q1: What are the indications for intervention in chronic pancreatitis	1.1 Endoscopic or surgical treatment should be offered to patients with chronic pancreatitis with persistent severe pain. Intervention in the form of either surgery or endotherapy is not recommended in asymptomatic patients with chronic pancreatitis who do not have abdominal pain to improve pancreatic exocrine and/or endocrine function or prevent cancer.	1.00	Moderate	Strong	Strong
Q1: What are the indications for intervention in chronic pancreatitis	1.2 Endoscopic or surgical treatment should be carried out after careful patient selection for local complications of chronic pancreatitis with persistent clinical symptoms such as gastric outlet obstruction, duodenal stenosis, biliary obstruction with cholestasis and pseudocysts	1.00	Moderate	Strong	Strong
Q9: What is the strategy for the treatment of duodenal obstruction in chronic pancreatitis.	9.2 Duodenal stenosis due to chronic pancreatitis should be carefully differentiated from pancreatic cancer.	1.00	Moderate	Strong	Strong
Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.	5.1 For pancreatic pseudocysts that cause symptoms and/or complications, interventional or surgical treatment should be performed.	0.94	Moderate	Strong	Strong
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.6 Surgical treatment should be planned if bile duct obstruction reoccurs after one year of endoscopic stent treatment. For the patients who have significant calcifications and/or mass of the pancreatic head, surgical treatment may be preferred as an initial treatment.	0.94	Low	Strong	Strong
Q8: What is the strategy for the treatment of hemosuccus pancreaticus in chronic pancreatitis.	8.1 Percutaneous endovascular treatment should be the first choice of treatment for hemosuccus pancreaticus in hemodynamically stable patients. However, patients with hemodynamic instability and unsuccessful embolization should undergo surgery.	0.94	Low	Conditional	Strong
Q 2: What is the best strategy for the treatment of pancreatic ductal stricture.	2.1 Non-surgical decompression of the main pancreatic duct including endoscopic therapy can be selected for immediate pain relief of chronic pancreatitis before considering surgery. Surgical intervention should be considered if endoscopic procedure fails or has temporary success needing repeated endoscopic therapy	0.88	Moderate	Conditional	Strong
Q 3: How should endoscopic stent treatment be done for pancreatic ductal stricture.	3.1 A straight plastic pancreatic stent should be placed across the stricture depending on the caliber of the stricture of the pancreatic duct.	0.88	Low	Conditional	Strong
Q 3: How should endoscopic stent treatment be done for pancreatic ductal stricture.	3.2 An endoscopic retrograde cholangio-pancreatography (ERCP) inserted endoscopic stent should be removed or exchanged at between 2 and 3 months later. At this time a new stent should be inserted if there is still a significant stricture.	0.88	Low	Conditional	Strong
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.1 Endoscopic treatment is recommended when the patients show symptoms related to the distal bile duct obstruction (obstructive jaundice and/or acute cholangitis), and in persistent cholestasis with alkaline phosphatase elevation ($>2-3$ times) for at least month even in asymptomatic patients.	0.88	Low	Conditional	Strong
Q7: What is the strategy for the treatment of internal pancreatic fistula and pancreatic pleural effusion and ascites in chronic pancreatitis.	7.1 Endoscopic interventional therapy should be undertaken for the management of internal pancreatic fistula in patients presenting with main pancreatic duct disruption or obstruction.	0.88	Low	Conditional	Strong
Q9: What is the strategy for the treatment of duodenal obstruction in chronic pancreatitis.	9.1 Surgical treatment is recommended for duodenal stenosis associated with chronic pancreatitis, as endoscopic treatment is difficult in such cases.	0.88	Moderate	Conditional	Strong
Q 2: What is the best strategy for the treatment of pancreatic ductal stricture.	2.3 Endoscopic drainage should be the preferred modality for treating pancreatic pain and biliary stricture in patients with chronic pancreatitis who have associated portal/splenic vein thrombosis.	0.82	Moderate	Conditional	Strong
Q4: What is the strategy for the treatment of pancreatic ductal stones.	4.2 Endoscopic extraction is indicated for small stones or stone fragments after ESWL.	0.82	Moderate	Conditional	Strong
Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.	5.5 Surgical intervention should be considered if endoscopic drainage of pseudocysts fails or has temporary success needing repeated endoscopic therapy, especially when there is disconnected duct syndrome, inflammatory mass, and intraductal calculi with duct strictures.	0.82	Low	Conditional	Strong
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.5 Endoscopic placement of multiple plastic or covered metal stent and/or surgery are appropriate to manage refractory bile duct obstruction.	0.76	Low	Conditional	Conditional
Q4: What is the strategy for the treatment of pancreatic ductal stones.	4.1 ESWL should be the first-line therapy as non-surgical intervention for main pancreatic duct stones in patients with chronic pancreatitis who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain.	0.71	Low	Conditional	Conditional
Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.	5.2 Underlying stricture or disruption of the main pancreatic duct with symptoms and/or complications should be treated with endoscopic transpapillary placement of a pancreatic stent for	0.71	Moderate	Conditional	Conditional

Table 1 (continued)

Domain	Statement	α	Quality score	Recommendation	Agreement
	pseudocysts <5 cm and with communication with the main pancreatic duct.				
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.2 Endoscopic treatment with multiple plastic or covered metal stents may be effective for relieving of the symptoms related to the distal bile duct obstruction due to chronic pancreatitis.	0.71	Low	Weak	Conditional
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.4 Plastic stent replacement for main biliary duct stricture is recommended every 3 months. The optimal period for replacement of covered metal stent is currently unknown.	0.71	Low	Weak	Conditional
Q6: What is the strategy for the treatment of distal main biliary duct obstruction in chronic pancreatitis.	6.3 In main biliary duct strictures caused by chronic pancreatitis, biliary stent placement is recommended for a period of 6 months to 1 year.	0.65	Low	Weak	Weak
Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.	5.3 Asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter that do not resolve within six weeks may be treated with transmural drainage.	0.53	Low	Weak	Weak
Q5: What is the strategy for the treatment of pancreatic pseudocysts in chronic pancreatitis.	5.4 In case of a suspected neoplastic cystic lesion diagnostic needle aspiration of the cyst may be done.	0.53	Low	Weak	Weak
Q 2: What is the best strategy for the treatment of pancreatic ductal stricture.	2.2 If there are contraindications for surgical therapy in patients in whom conventional endoscopic therapy has failed, endosonographic-guided drainage of the pancreatic duct is another option for pain control.	0.47	Moderate	Weak	Weak
Q 3: How should endoscopic stent treatment be done for pancreatic ductal stricture.	3.3 Multiple stents or a metal stent may be considered for persisting pancreatic strictures due to severe chronic pancreatitis.	0.47	Low	Conditional	Weak
Q1: What are the indications for intervention in chronic pancreatitis.	1.3 Celiac plexus block may be undertaken in patients for significant abdominal pain who are not candidates for pancreatic surgery or have not responded to endotherapy and extracorporeal shock wave lithotripsy (ESWL), or have a poor general condition as a temporizing measure before definitive therapy.	0.41	Moderate	Weak	Weak

for different subsets of CP (eg, multifocal strictures, large calcific burden, etc.), and that randomized controlled trial level data are needed.

Clinical practice should be consolidated around the strong recommendations. Where the recommendations are weak clinical practice should be curtailed or substantially modified, unless new good evidence emerges. Interventions with conditional support should be considered focus areas for active research to produce further quality evidence to strengthen the particular clinical approach.

Declaration of competing interest

All authors have no conflict of interest of these consensus guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2020.05.022>.

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